

Remarks Regarding New Claims:

Amendments to Claims 1, 4 and 5 are for purposes of conforming the claims to the elected species only and are supported by pages 15 and 19 of the specification.

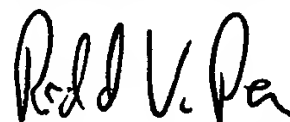
RESPONSE

Election/Restriction

The Applicants elect Group I, with Example 1 as a species--wherein A is a five-membered monocyclic heterocyclic ring consisting of one ring nitrogen and V is a carbocyclic radical--with traverse.

Applicants respectfully submit that no serious burden is imposed upon the Examiner by not restricting the claims, because the Examiner has not shown how a search of Groups I and II would be any more burdensome than a search of Group I alone. Therefore, Applicants respectfully request that the restriction requirement be withdrawn.

Respectfully submitted,



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Marked-up changes:

Page 3, first full paragraph:

Integrin $\alpha_v\beta_6$ is an RGD, tenascin and fibronectin binding protein (J. Biol. Chem. 267:5790-6, 1992) which is expressed by a number of cells, such as carcinoma and epithelial cells, and is thought to be involved in carcinoma cell proliferation (J. ~~Biol. Chem.~~ **Cell Biol.** 127:547-56, 1994), in wound healing and cell attachment (J. Invest. Dermatol. 106:42-8, 1996), in epithelial inflammation, such as asthma (J. Cell Biol. 133:921-928, 1996), in inducing gelatinase B secretion, activation of the protein kinase-C pathway, tumor cell spreading and proliferation in colon cancer cells (Biochem. Biophys. Res. Commun. 249:287-291, 1998; Int. J. Cancer 81:90-97, 1999), in regulation of pulmonary inflammation and fibrosis and binding and activating transforming growth factor β_1 (Munger et al., Cell (Cambridge, Mass) 96:319-328, 1999), and in viral infections (Virology 239:71-77, 1997).

1. (Amended) A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein g, h and j are each independently 0 or 1; provided when h is 0, then g is 0;

each Alk is independently a alkyl radical;

U represents amidino, guanidino, $-(G-alkyl)_k-NH-R_1$, $-(G-alkyl)_k-NH-C(Q)-R_1$, $-(G-alkyl)_k-C(Q)-N(R)-R_1$, $-(G-alkyl)_k-NH-C(Q)-N(R)-R_1$, $-(G-alkyl)_k-NH-C(Q)-O-R_1$ or $-(G-alkyl)_k-O-C(Q)-N(R)-R_1$ radical; or U represents a hydroxyalkyl-G- radical which is optionally substituted by a cycloalkyl, aryl, heteroaryl or heterocyclyl, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2 ;

wherein k is 0 or 1;

G represents a bond, O, S or NH;

Q represents O, S, NH, N-CN or N-alkyl;

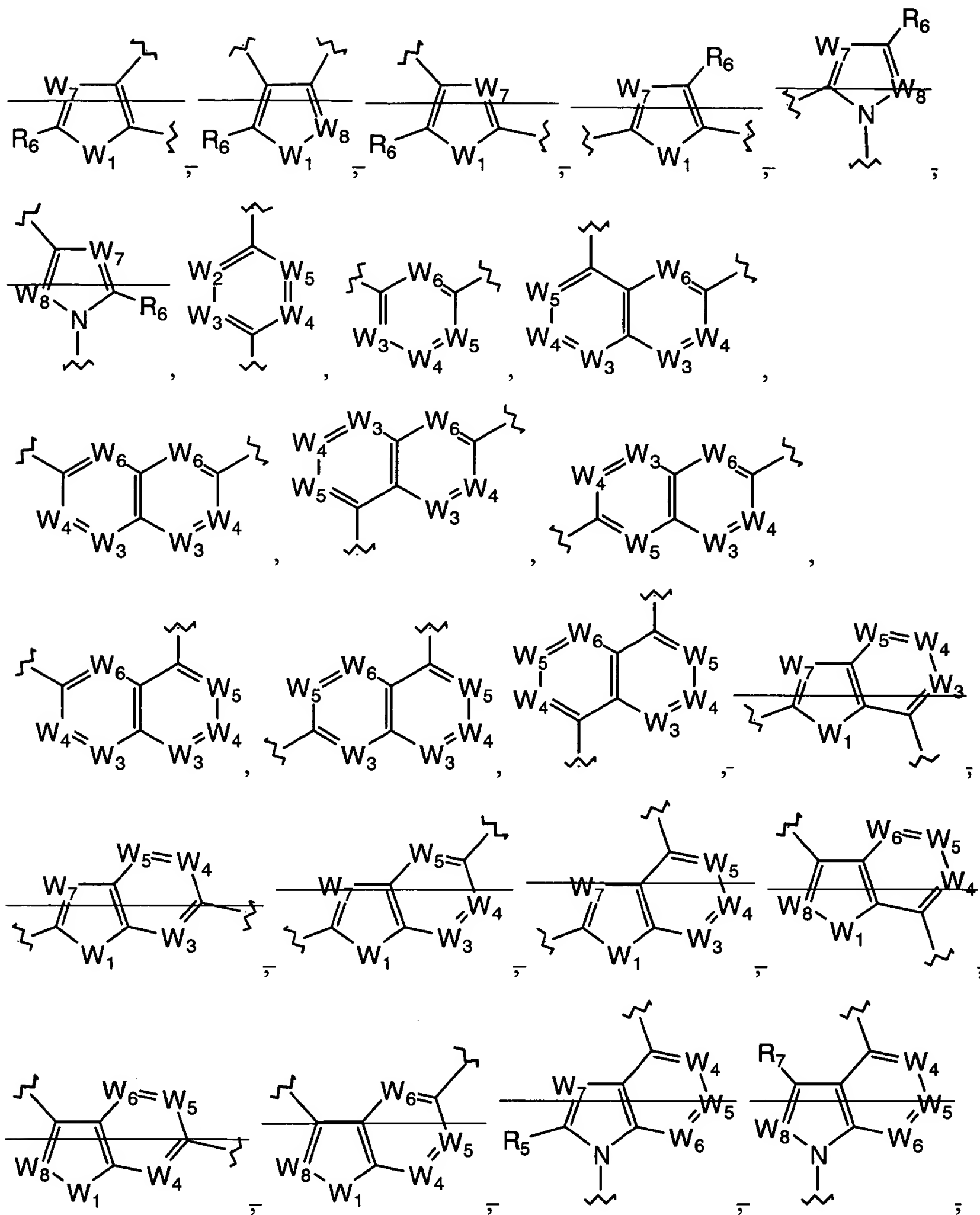
R is a radical of hydrogen or alkyl;

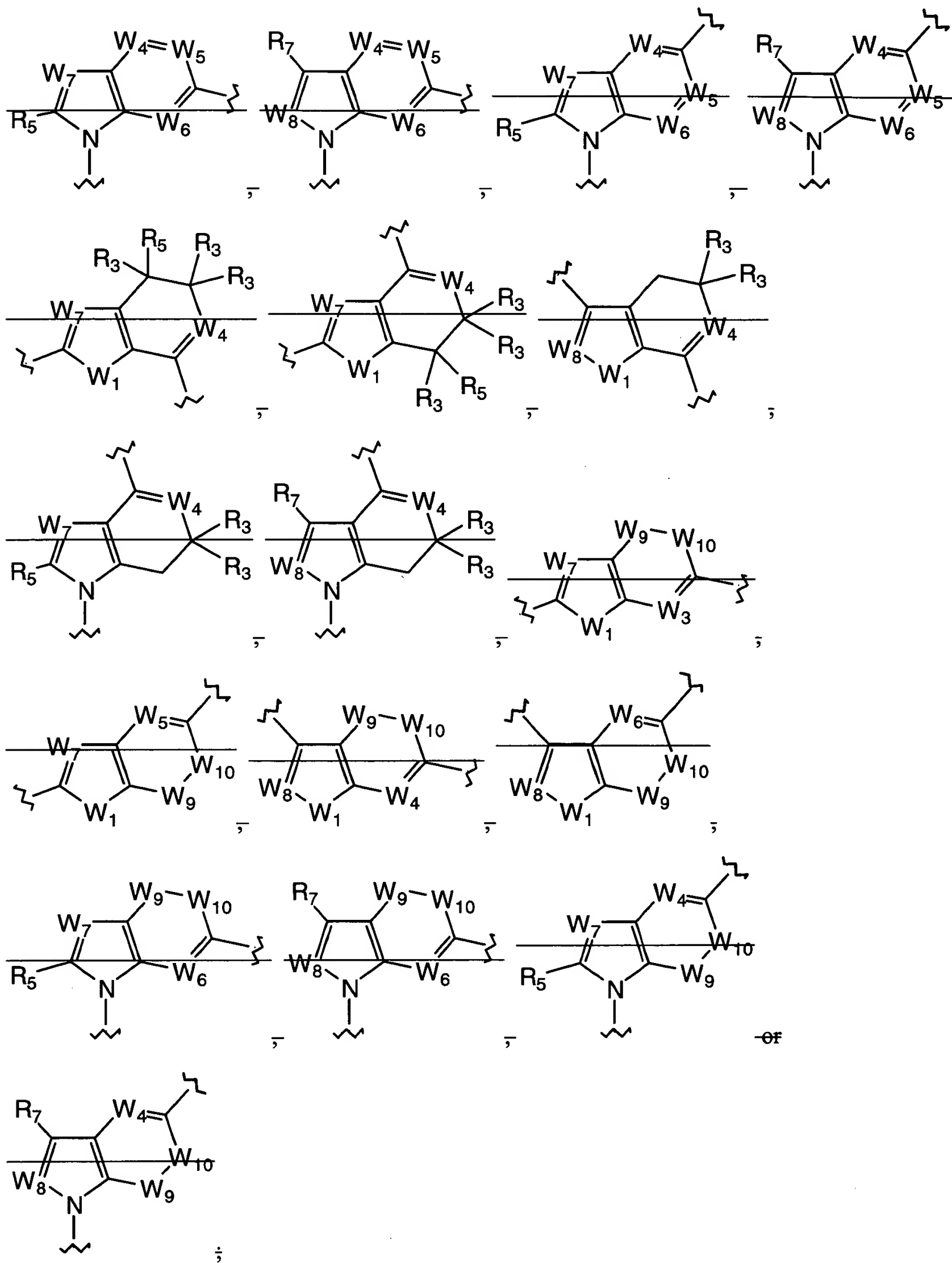
R₁ is a radical of alkyl, haloalkyl, R₂₁R₂₂N-alkyl, R₂₁O-alkyl, R₂₁S-alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, aryl-alkyl, heteroaryl, heteroaryl-alkyl, heterocyclyl or heterocyclyl-alkyl, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R₂;

wherein R₂₁ and R₂₂ are each independently a radical of hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkyl-alkyl, aryl, aryl-alkyl, heteroaryl, heteroaryl-alkyl, heterocyclyl or heterocyclyl-alkyl, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R₂;

each R₂ is independently a halo, alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, hydroxy, carboxy, cyano, azido, amidino, guanidino, nitro, amino, alkylamino or dialkylamino radical or two adjacent R₂ radicals on an aryl or heteroaryl radical represent a methylenedioxy, ethylenedioxy or propylenedioxy radical;

V represents a radical of formula





wherein ~~W₁ is O, S or N-R₃; wherein each R₃ is independently a hydrogen or alkyl radical; W₇ is N or C-R₇; W₈ is N or C-R₅;~~

~~W₉ is C(R₃)₂ and W₁₀ is W₁; or W₉ is CR₃R₅ and W₁₀ is C(R₃)₂;~~

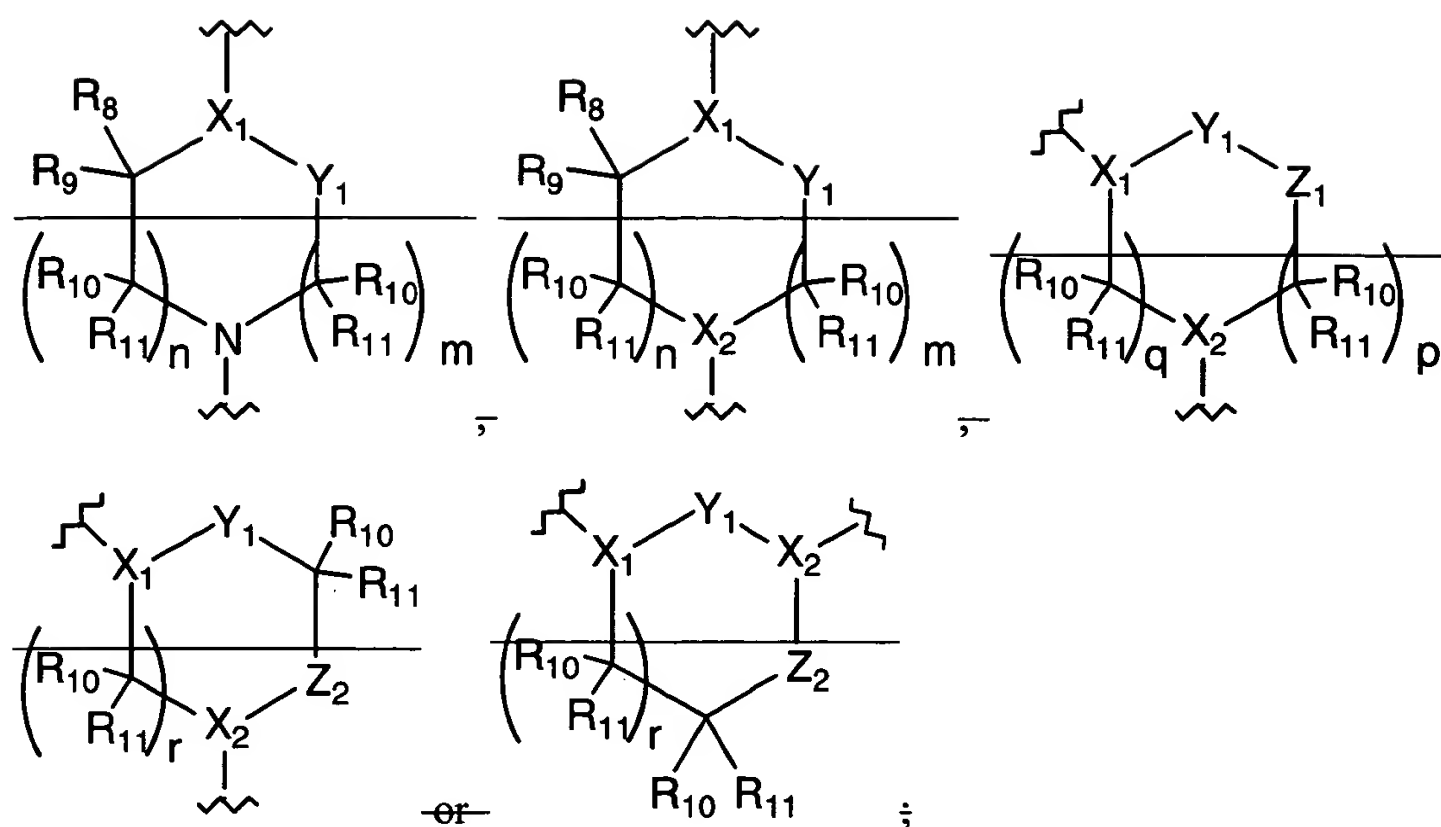
each W₂, W₃, W₄ and W₅ ~~are independently N or~~ is C-R₄; provided the total number of cycloalkyl, aryl, heteroaryl, heterocyclyl, carboxy, -C(O)-O-R₁₉, -C(O)-R₁₉, -C(O)-NH-R₁₉, -C(O)-N(R₁₉)₂ and -R₁₉ radicals in W₂, W₃, W₄ and W₅ is 0-2;

each W₆ ~~is independently N or C-H; provided that not more than two of W₂, W₃, W₄, W₅ and W₆ represent N;~~ and

each R₄ is independently a hydrogen, halo, alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, hydroxy, cyano, carboxy, -C(O)-O-R₁₉, -C(O)-R₁₉, -C(O)-NH-R₁₉, -C(O)-N(R₁₉)₂, cycloalkyl, cycloalkyl-alkyl, aryl, aryl-alkyl, heteroaryl, heteroaryl-alkyl, heterocyclyl or heterocyclyl-alkyl radical, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R₂; or two adjacent R₄ radicals taken together with the carbon atoms to which they are attached represent a fused-phenyl or fused-heteroaryl of 5-6 ring members, wherein the phenyl and heteroaryl radicals are optionally substituted by 1-3 radicals of R₂;

R₅, R₆ and R₇ are each independently a hydrogen, halo, alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, hydroxy or cyano radical; or R₅ and R₆ or R₆ and R₇ taken together with the carbon atoms to which they are attached represent a fused-phenyl or fused-heteroaryl of 6 ring members, wherein the phenyl and heteroaryl radicals are optionally substituted by 1-3 radicals of R₂; or R₃ and R₆ taken together with the carbon atoms to which they are attached represent a fused-heteroaryl of 6 ring members optionally substituted by 1-3 radicals of R₂;

A represents a radical of formula



wherein X_1 is N or C-H;

X_2 is C-H, C-alkyl, a spirocycloalkyl or spiroheterocyclyl radical; wherein the spirocycloalkyl and spiroheterocyclyl radicals are optionally substituted by an oxo or thiooxo radical and 1-2 radicals of alkyl, haloalkyl, hydroxy, alkoxy or haloalkoxy;

Y_1 is C(O), C(S), S(O) or S(O)₂;

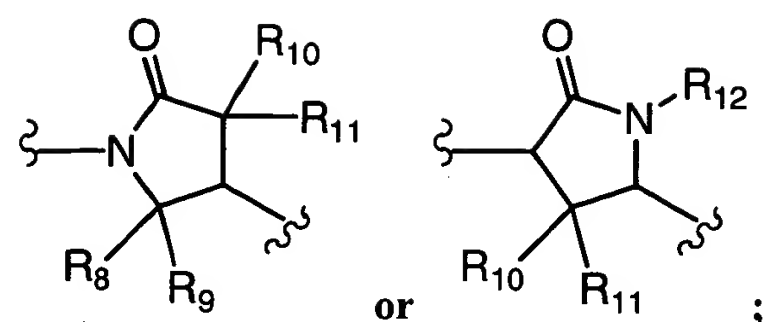
Z_1 is O or N-R₁₂;

Z_2 is O, S or N-R₁₂;

n and m are each independently 0, 1 or 2, provided n + m = 1, 2, 3 or 4;

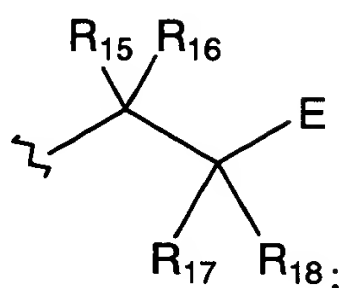
p and q are each independently 0, 1 or 2, provided p + q = 1, 2 or 3;

r is 1 or 2;



R_8 , R_9 , R_{10} , R_{11} and R_{12} are each independently a hydrogen or alkyl radical; or $-CR_8R_9-$ represents a $-C(O)-$;

B represents a radical of formula



wherein (a) R_{15} is a hydrogen or alkyl radical; and R_{17} is (1) an aryl, heteroaryl, $-NH-C(O)-R_{19}$, $-C(O)-NH-R_{19}$, $-NH-C(O)-NH-R_{19}$, $-O-C(O)-NH-R_{19}$, $-NH-C(O)-O-R_{19}$, $-S(O)_2-R_{19}$, $-NH-S(O)_2-R_{19}$, $-S(O)_2-NH-R_{19}$ or $-NH-S(O)_2-NH-R_{19}$ radical, or (2) an alkyl radical substituted by a radical of aryl, heteroaryl, $-NH-C(O)-R_{19}$, $-C(O)-NH-R_{19}$, $-NH-C(O)-NH-R_{19}$, $-O-C(O)-NH-R_{19}$, $-NH-C(O)-O-R_{19}$, $-S(O)_2-R_{19}$, $-NH-S(O)_2-R_{19}$, $-S(O)_2-NH-R_{19}$ or $-NH-S(O)_2-NH-R_{19}$; wherein the aryl and heteroaryl radicals are optionally substituted by 1-3 radicals of R_2 ; or

(b) R_{17} is a hydrogen or alkyl radical; and R_{15} is (1) an aryl, heteroaryl, cycloalkyl, heterocyclyl, $-NH-C(O)-R_{19}$, $-C(O)-NH-R_{19}$, $-NH-C(O)-NH-R_{19}$, $-O-C(O)-NH-R_{19}$, $-NH-C(O)-O-R_{19}$, $-S(O)_2-R_{19}$, $-NH-S(O)_2-R_{19}$, $-S(O)_2-NH-R_{19}$ or $-NH-S(O)_2-NH-R_{19}$ radical, or (2) an alkyl radical substituted by a radical of aryl, heteroaryl, cycloalkyl, heterocyclyl, $-NH-C(O)-R_{19}$, $-C(O)-NH-R_{19}$, $-NH-C(O)-NH-R_{19}$, $-O-C(O)-NH-R_{19}$, $-NH-C(O)-O-R_{19}$, $-S(O)_2-R_{19}$, $-NH-S(O)_2-R_{19}$, $-S(O)_2-NH-R_{19}$ or $-NH-S(O)_2-NH-R_{19}$ radical; wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2 ;

provided that when a nitrogen atom is attached to the carbon atom to which R_{15} is attached, then R_{15} is (1) an aryl, heteroaryl, cycloalkyl, heterocyclyl or $-C(O)-NH-R_{19}$ radical, or (2) an alkyl radical substituted by a radical of aryl, heteroaryl, cycloalkyl, heterocyclyl, $-NH-C(O)-R_{19}$, -

$C(O)-NH-R_{19}$, $-NH-C(O)-NH-R_{19}$, $-O-C(O)-NH-R_{19}$, $-NH-C(O)-O-R_{19}$, $-S(O)_2-R_{19}$, $-NH-S(O)_2-R_{19}$, $-S(O)_2-NH-R_{19}$ or $-NH-S(O)_2-NH-R_{19}$;

wherein R_{19} is a alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, aryl-alkyl, heteroaryl, heteroaryl-alkyl, heterocyclyl or heterocyclyl-alkyl, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2 ;

R_{16} and R_{18} are each independently a hydrogen or alkyl radical; and

E is a radical of carboxy, amido, tetrazolyl, $-C(O)-O-R_{20}$, $-C(O)-NH-R_{20}$, $-C(O)-NH-S(O)-R_{20}$, $-C(O)-NH-S(O)_2-R_{20}$ or $-C(O)-NH-C(O)-R_{20}$;

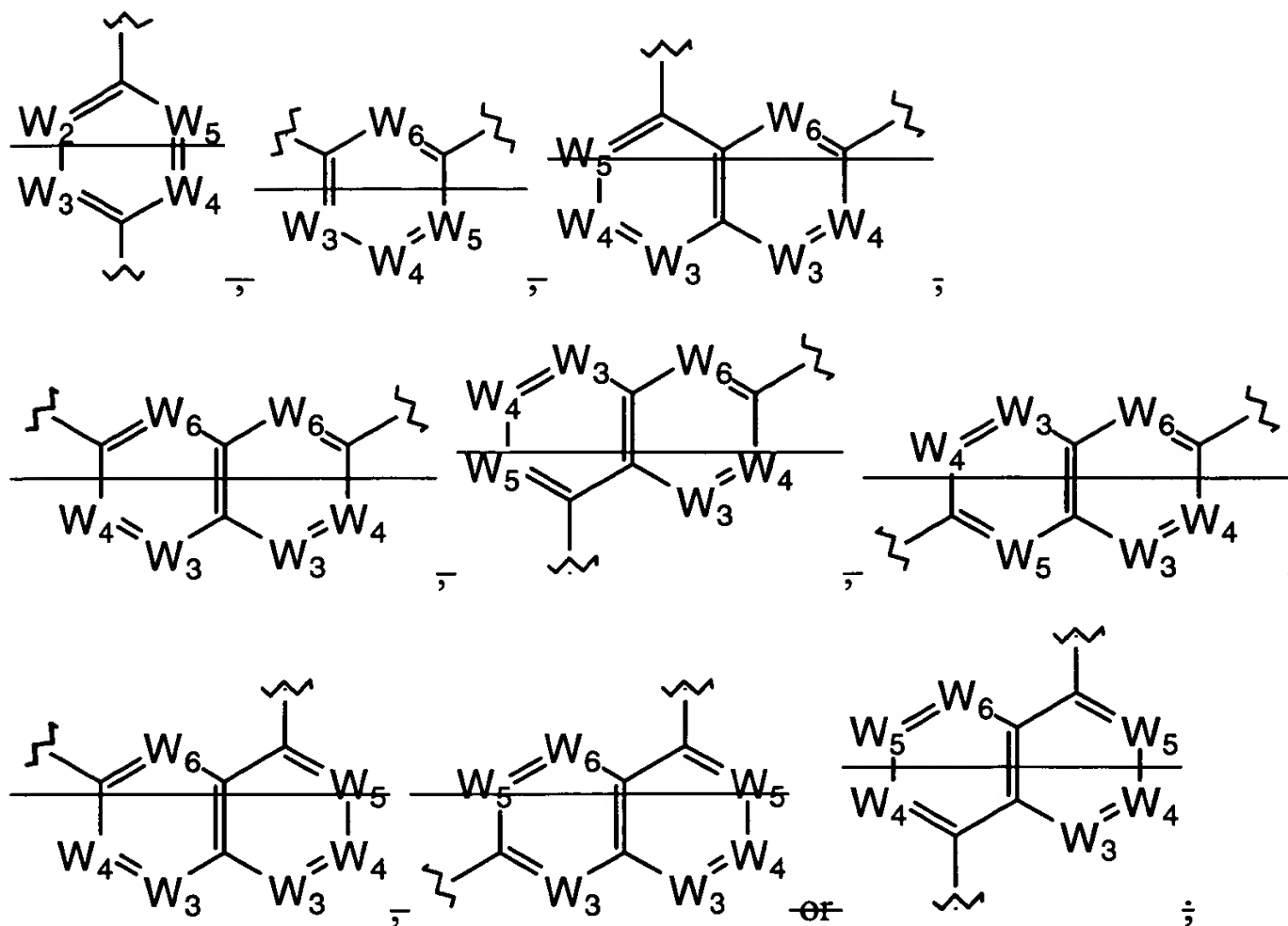
wherein R_{20} is an alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl radical or an alkyl radical substituted by 1-3 radicals of halo, hydroxy, carboxy, amino, cycloalkyl, aryl, heteroaryl or heterocyclyl, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2 ; and

provided that when U represents amidino, guanidino, $-C(Q)-NH-R_1$ or $-NH-C(Q)-NH-R_1$ radical, wherein Q represents NH, N-CN or N-alkyl, then at least one of g, h or j is 1.

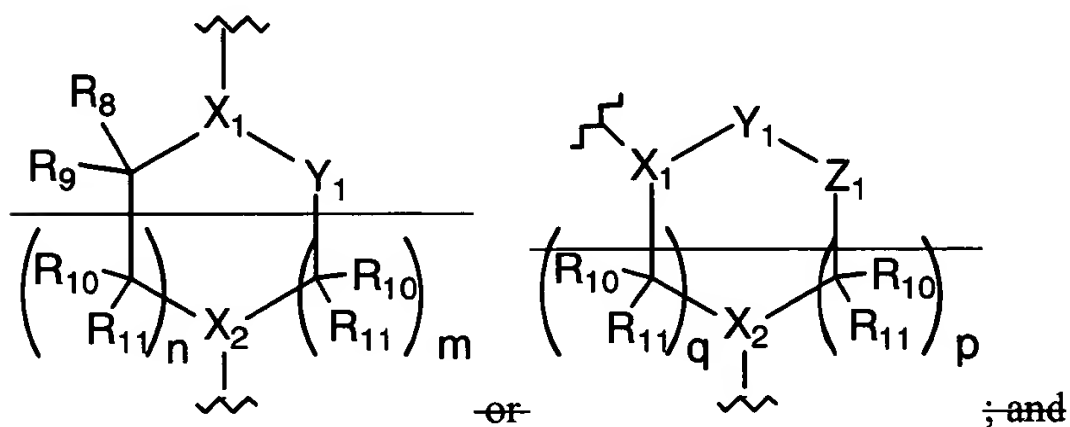
~~3. (Delete) The compound of Claim 2 or a pharmaceutically acceptable salt thereof, wherein~~

~~each Alk is independently a C_4-C_8 alkyl radical;~~

~~V represents a radical of formula~~



A represents a radical of formula

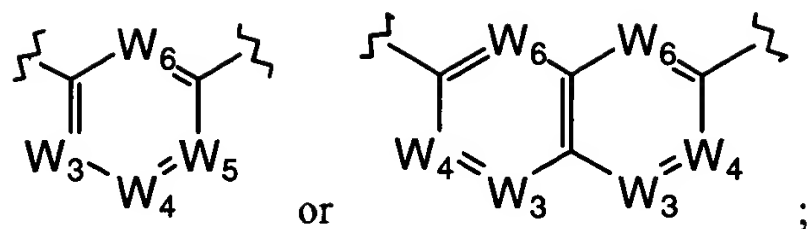


Y₁ is ~~C(O)~~ or ~~C(S)~~.

4. (Amended) The compound of Claim 2 or a pharmaceutically acceptable salt thereof, wherein

each Alk is independently a C₁-C₆ alkyl radical;

V represents a radical of formula



~~X₂ is C-H or C-(methyl) radical;~~

~~Y₁ is -C(O)-; and~~

R₈, R₉, R₁₀, R₁₁ and R₁₂ are each independently a hydrogen or methyl radical; or -CR₈R₉- represents a -C(O)-.

5. (Amended) The compound of Claim 4 or a pharmaceutically acceptable salt thereof, wherein

each Alk is independently a C₁-C₄ alkyl radical;

U represents amidino, guanidino, -(G-(C₁-C₈ alkyl))_k-NH-R₁, -(G-(C₁-C₈ alkyl))_k-NH-C(Q)-R₁, -(G-(C₁-C₈ alkyl))_k-C(Q)-N(R)-R₁, -(G-(C₁-C₈ alkyl))_k-NH-C(Q)-N(R)-R₁ or -(G-(C₁-C₈ alkyl))_k-NH-C(Q)-O-R₁ radical;

G represents a bond, O or NH;

Q represents O, S, NH, N-CN or N-(C₁-C₄ alkyl);

R is a radical of hydrogen or C₁-C₄ alkyl;

R₁ is a radical of C₁-C₆ alkyl, halo(C₁-C₆ alkyl) of 1-5 halo radicals, R₂₁R₂₂N-(C₁-C₆ alkyl), R₂₁O-(C₁-C₆ alkyl), C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl(C₁-C₆ alkyl), aryl, aryl(C₁-C₆ alkyl), heteroaryl of 5-10 ring members, heteroaryl(C₁-C₆ alkyl) of 5-10 ring members, heterocyclyl of 5-8 ring members or heterocyclyl(C₁-C₆ alkyl) of 5-8 ring members, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R₂;

R_{21} and R_{22} are each independently a radical of hydrogen, C_1 - C_8 alkyl, aryl, aryl(C_1 - C_4 alkyl), heteroaryl of 5-10 ring members or heteroaryl(C_1 - C_4 alkyl) of 5-10 ring members, wherein the aryl and heteroaryl radicals are optionally substituted by 1-3 radicals of R_2 ;

each R_2 is independently a halo, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkylthio, halo(C_1 - C_2 alkyl) of 1-5 halo radicals, halo(C_1 - C_2 alkoxy) of 1-5 halo radicals, hydroxy, carboxy, cyano, azido, amidino, guanidino, nitro, amino, C_1 - C_4 alkylamino or di(C_1 - C_4 alkyl)amino radical or two adjacent R_2 radicals on an aryl or heteroaryl radical represent a methylenedioxy, ethylenedioxy or propylenedioxy radical;

~~each W_6 is $C-H$;~~

each R_4 is independently a hydrogen, halo, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkylthio, halo(C_1 - C_2 alkyl) of 1-5 halo radicals, halo(C_1 - C_2 alkoxy) of 1-5 halo radicals, hydroxy, cyano, carboxy, -C(O)-O- R_{19} , -C(O)- R_{19} , -C(O)-NH- R_{19} , -C(O)-N(R_{19})₂, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyl(C_1 - C_4 alkyl), aryl, aryl(C_1 - C_4 alkyl), heteroaryl of 5-10 ring members, heteroaryl(C_1 - C_4 alkyl) of 5-10 ring members, heterocyclyl of 5-8 ring members or heterocyclyl(C_1 - C_4 alkyl) of 5-8 ring members radical, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2 ; and

R_{20} is a C_1 - C_4 alkyl, aryl or heteroaryl of 5-10 ring members or a C_1 - C_4 alkyl radical substituted by 1-3 radicals of halo, hydroxy, carboxy, amino, aryl, heteroaryl of 5-10 ring members or heterocyclyl of 5-8 ring members, wherein the aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R_2 .